Correlation between imaging studies and histological analysis in the assessment of microvascularization in lipedema

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ABSTRACT

Objective: To evaluate microvascular alterations in lipedema using a multimodal approach combining microflow imaging (MFI) ultrasound, infrared thermography, standardized clinical photography, and histological analysis.

Methods: Twelve women with clinically diagnosed lipedema involving the lower limbs (types III and IV, stages II-III) were included. Vascular assessment was performed using high-resolution ultrasound imaging with advanced Doppler (MFI) to detect low-velocity microvascular flow. Infrared thermography was used to identify abnormal thermal patterns, and standardized clinical photographs documented morphological changes. Punch biopsies (6 mm) from the lateral thigh were analyzed histologically using hematoxylin and eosin, periodic acid-Schiff, trichrome, picrosirius red, Giemsa, and Perls' stains.

Results: Ultrasound examination demonstrated increased subcutaneous thickness, connective tissue disorganization, and nonencapsulated hypoechoic nodules. MFI with spectral analysis revealed low-resistance arterial flow (resistance index <0.7) in microvessels surrounding these nodules, suggesting inflammatory activity. Thermography showed regional thermal differences (ΔT) between 0.5 °C and 0.7 °C, with focal hyperthermia indicating inflammation and areas of relative hypoperfusion suggesting microvascular stasis or fibrosis. All patients exhibited thermographic patterns consistent with altered cutaneous perfusion. Of 13 biopsy samples collected, 10 were analyzed. All samples showed adipose tissue hyperplasia with variable adipocyte size. Increased capillary density and mast cell infiltration were observed in 60% of cases, cytosteatonecrosis in 30%, and septal fibrosis in 10%.

Conclusions: Lipedema is associated with microvascular and inflammatory alterations that can be detected by noninvasive imaging techniques. The combined use of MFI ultrasound and infrared thermography correlates with histological evidence of increased capillary density and inflammation, supporting the presence of an active inflammatory microangiopathy. This multimodal approach may enhance diagnostic evaluation and clinical monitoring of patients with lipedema. (JVS-Vascular Insights 2026;4:100412.)

Keywords: Lipedema; Microvessels; Ultrasonography; Doppler; Color; Thermography; Capillaries; Inflammation

Lipedema is a chronic adipose tissue disorder that affects almost exclusively women and is characterized by symmetrical accumulation of subcutaneous fat in the limbs, pain on palpation, easy bruising, and body disproportion—features that frequently lead to misdiagnosis as obesity or lymphedema.[1–4] In recent years, multiple studies have demonstrated that lipedema is not merely a fat deposition disorder but a condition in which fluid, fat, and fibrosis interact in a complex manner within a shared inflammatory microenvironment.[1,3,5,6]

Among the relevant recent findings is the identification of an inflammatory microangiopathy in the affected adipose tissue, characterized by increased capillary density, vascular wall thickening, focal angiogenesis, and macrophage infiltration.[7] Histological and ultrastructural analyses have also confirmed early endothelial cell alterations, including hyperplasia and degeneration, suggesting that capillary barrier dysfunction may precede the characteristic adipose tissue expansion observed in the disease.[8]

These endothelial alterations have been accompanied, in functional experiments, by increased vascular permeability, possibly induced by mediators secreted by the stromal vascular fraction of adipose tissue in patients

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with lipedema. Studies have demonstrated that this secretome reduces the expression of vascular endothelial-cadherin, a protein essential for endothelial junction integrity, contributing to fluid extravasation and activation of proadipogenic pathways.[9] In parallel, increased vascular endothelial growth factor C levels and macrophage infiltration have been observed without major structural alterations in lymphatic vessels, reinforcing the concept of increased vascular permeability within an otherwise functional lymphatic system.[10]

In the dermal compartment, the presence of dilated interstitial spaces and accumulation of protein-rich fluid further support the role of a microangiopathy associated with local congestion.[11] At the systemic level, circulating biomarkers such as platelet factor 4 have recently been described as potential indicators of lymphatic dysfunction and have been found to be elevated in patients with lipedema, linking the disease to a broader lymphovascular spectrum.[12]

In the field of imaging, noncontrast magnetic resonance lymphography has demonstrated subtle differences between pure lipedema and mixed forms with lymphedema, including lymphatic dilatation and delayed flow in more advanced stages.[2] However, objective methods capable of correlating imaging findings with histological alterations remain limited. Ultrasound techniques sensitive to slow blood flow—such as superb microvascular imaging, microflow imaging (MFI; Philips Medical Systems), and ultra micro angiography (UMA; Mindray Medical Systems)—have shown correlations between microvascular flow indices and vessel density in tumor biopsies, opening the possibility of their application in adipose tissue disorders.[13,14]

Within this context, investigating whether imaging parameters obtained using MFI and infrared thermography correlate with histological alterations of microvascularization and inflammation in lipedema may provide new noninvasive biomarkers, supporting differential diagnosis and clinical monitoring of this condition. We hypothesized that imaging-based microvascular findings detected by MFI and thermography would correspond to histologic evidence of angiogenesis and inflammatory microangiopathy in lipedema tissue.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, prospective case series
- **Key Findings:** In 12 women with stage II-III lipedema, microflow imaging demonstrated low-resistance microvascular arterial flow (resistance index < 0.7), and thermography showed thermal gradients of 0.5 °C to 0.7 °C. Histology confirmed increased capillary density and mast cell infiltration in 60% of samples.
- **Take Home Message:** Ultrasound-derived microflow imaging and infrared thermography correlate with histologic evidence of inflammatory microangiopathy in lipedema and may serve as noninvasive biomarkers for disease characterization and monitoring.

OBJECTIVES

The objective of this study was to evaluate the correlation between imaging findings and histological data in patients with lipedema, aiming to determine whether microvascular alterations detected by ultrasound microvascular imaging with MFI and infrared thermography reflect structural changes in adipose tissue.

METHODS

Study design and participants

This study was designed as a case series including women diagnosed with lipedema stages II and III, according to the clinical criteria established by Wold and Herbst.[15] Patients with a confirmed clinical diagnosis of lipedema were included regardless of body mass index (BMI). Patients with primary lymphedema, secondary lymphedema, or lipolymphedema (stage IV) were excluded, as the presence of associated lymphedema was considered an exclusion criterion.

All participants underwent a standardized evaluation protocol consisting of clinical examination, ultrasound Doppler imaging associated with MFI, infrared thermography, and adipose tissue biopsy. Samples were obtained from the lateral aspect of the thigh, a region considered representative of tissue involvement in lipedema.

The research protocol followed the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of the Health Sciences Center of the Federal University of Espírito Santo (protocol No. 85778424500005060). All participants received detailed information about the study objectives and procedures, and written informed consent was obtained before inclusion.

The purpose of this study was not to evaluate diagnostic accuracy but to investigate biological correspondence between imaging biomarkers and histopathologic alterations within the same tissue region.

Imaging protocols

Ultrasound and MFI. Ultrasound examinations were performed using a Philips EPIQ Elite 10 system (Philips Medical Systems) with a high-frequency linear transducer (12 MHz).

All ultrasound examinations were performed by a vascular physician experienced in venous and lymphatic imaging and trained in microvascular Doppler techniques. The use of a single operator minimized interobserver variability, and acquisition parameters were standardized for all examinations to improve the reproducibility of microvascular flow detection.

The resistance index (RI) and microvascular flow imaging-derived vascular index (MFI-VI) were measured in representative subcutaneous areas and recorded in three distinct regions. Increased vascularization in these areas—uncommon in individuals without lipedema—associated with a low-resistance arterial flow PATTERN (RI $<$ 0.7) was considered suggestive of neovascularization and inflammatory activity.

Infrared thermography. Thermographic images were obtained using an FLIR E54 camera (FLIR Systems Inc). Anterior, lateral, and posterior views of the thighs were captured with the patient in the standing position.[16,17]

The thermal gradient (ΔT) between affected and adjacent regions was calculated, with values greater than 0.5 °C considered suggestive of local hyperperfusion.

Histological analysis

Skin and subcutaneous tissue fragments were obtained using 6-mm punch biopsies for histological analysis. Samples were fixed in buffered 10% formalin, embedded in paraffin, and sectioned at approximately 5 μm thickness. The following stains were performed: hematoxylin and eosin (H&E), Masson's trichrome (fibrosis), periodic acid-Schiff (basement membranes and capillaries), Giemsa (mast cells), and Perls' stain (hemosiderophages).

H&E staining was used for qualitative evaluation of the subcutaneous tissue, including capillary density, presence of fibrosis, and adipocyte hyperplasia. Mast cells and cytosteatonecrosis were quantitatively assessed using H&E staining, with mast cell counts performed per 10 high-power fields (×400, H&E and Giemsa) and confirmed by immunohistochemistry using CD117. Cytosteatonecrosis was classified as present or absent and confirmed by immunohistochemistry using CD68. No hemosiderophages were observed on Perls' staining.

Because this study was designed to correlate imaging findings with histologic alterations in clinically confirmed lipedema, the examiner was not blinded to the diagnosis in order to ensure correspondence between the imaged region and biopsy sampling site. Objective quantitative parameters were used to reduce observational bias.

Statistical analysis

Inferential statistical analysis was not performed because of the small sample size. Results were presented descriptively and exploratorily, emphasizing observational correlations between imaging findings (RI, ΔT, MFI-VI) and histological parameters. Means and ranges were used solely to illustrate general trends, without inference of statistical significance.

Limitations

Given the exploratory design aimed at correlating imaging with histology in clinically confirmed lipedema, the examiner was not blinded to diagnosis. This was necessary to ensure correspondence between the imaged region and the biopsy sampling site. Objective quantitative parameters (RI and ΔT) and standardized acquisition protocols were used to reduce observational bias.

RESULTS

Women with clinically diagnosed lipedema stages II-III were included. All patients demonstrated symmetric lower-limb involvement, pain on palpation, and increased subcutaneous thickness, confirming the clinical diagnosis.

Ultrasound and MFI. B-mode ultrasound imaging demonstrated increased subcutaneous thickness, disorganization of the connective tissue network, and thickening and discontinuity of the superficial fascia and connective fibers. Although conventional color Doppler did not reveal significant vascularization, the addition of MFI identified small vessels surrounding the connective tissue septa. Spectral analysis confirmed a low-resistance arterial flow pattern (RI $<$ 0.7) in all patients, with variable vessel density (Fig 1).

Infrared thermography. Thermographic assessment revealed significant alterations in cutaneous perfusion patterns, with thermal gradients (ΔT) ranging from 0.5 °C to 0.7 °C, compatible with tissue and vascular abnormalities. All patients demonstrated thermal amplitude values greater than 0.3 °C, indicating altered perfusion. Regions of focal hyperintensity corresponded to areas of inflammation and hyperemia, whereas zones of thermal hypoperfusion suggested microvascular stasis and fibrosis (Fig 2).

The heterogeneous thermal distribution, characterized by alternating regions of increased and decreased temperature, reflected localized perfusion imbalance consistent with MFI findings.

Histological findings. Histological analysis confirmed microvascular and inflammatory alterations of varying degrees. Increased capillary density was observed in 60% of samples, mast cell proliferation in 60%, cytosteatonecrosis in 30%, and mild fibrosis in 10%. Dilated capillaries, vascular wall thickening, and discrete to moderate inflammatory infiltrate were identified in the adipose stroma (Fig 3).

Correlation between imaging and histology. A descriptive correspondence was observed between imaging and histological findings. Patients exhibiting low-resistance flow patterns (RI $<$ 0.7) and higher thermal gradients showed increased capillary density and mast cell infiltration in the corresponding biopsy samples, suggesting that imaging parameters may reflect the degree of microvascular activity in affected tissue.

DISCUSSION

Inflammatory microangiopathy plays a central role in the pathophysiology of lipedema. The association

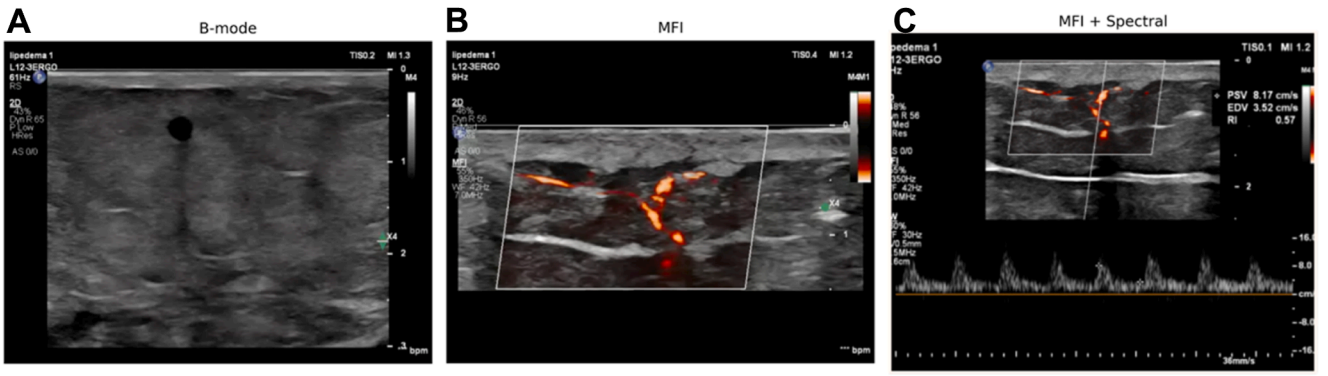
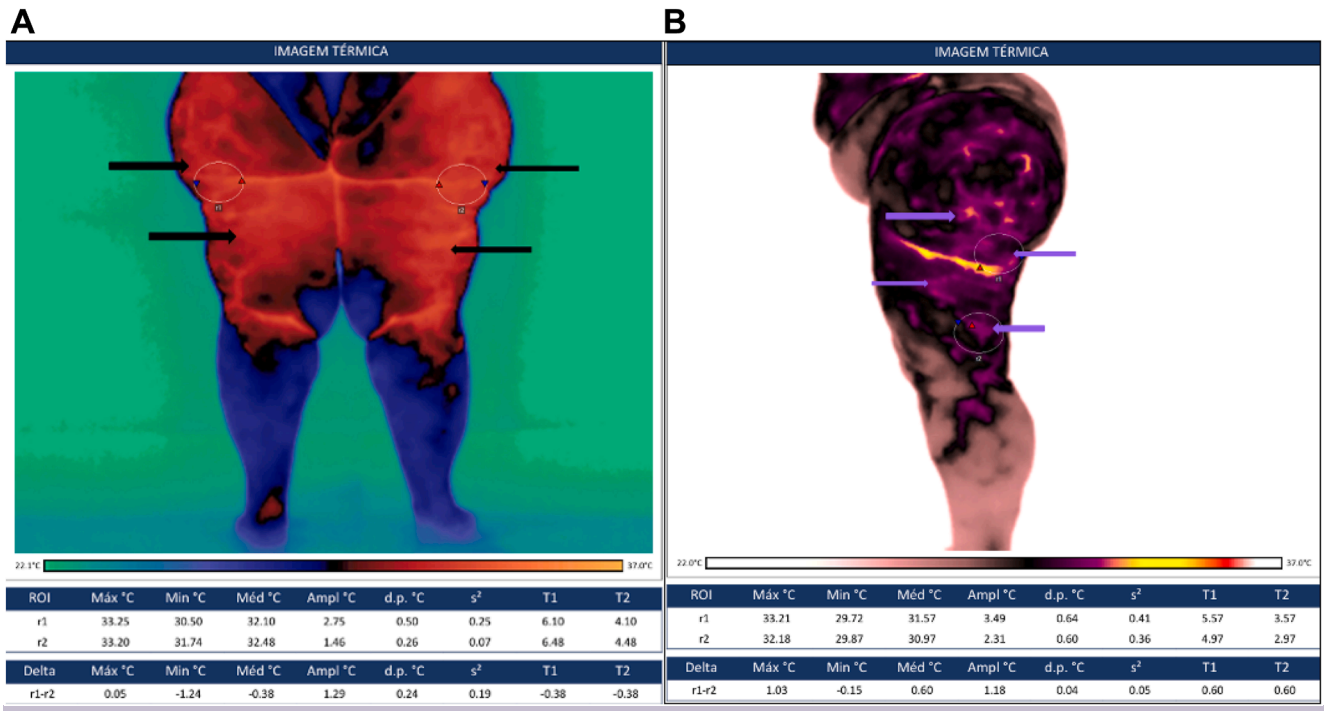


Fig 1. Ultrasound assessment of subcutaneous tissue in lipedema. **(A)** B-mode image demonstrating diffuse subcutaneous thickening and loss of architectural organization in the hypodermis. **(B)** Microflow imaging (MFI) showing discrete perinodular microvascular flow not visible with conventional color Doppler. **(C)** MFI combined with spectral Doppler demonstrating a low-resistance arterial flow pattern (resistance index [RI] 0.57), consistent with inflammatory hypervascularization.

between microvascular flow signals detected by MFI and increased capillary density observed on histology confirms that the hyperperfusion identified on imaging corresponds to underlying structural capillary alterations. These findings are consistent with the study by Al-Ghadban et al,[7] which demonstrated dilated microvessels, angiogenesis in approximately 30% of cases, increased macrophage infiltration, and adipocyte hypertrophy independent of BMI.

Infrared thermography adds a functional dimension to this evaluation by revealing thermal gradients ranging from 0.5 °C to 0.7 °C and mean thermal amplitude values greater than 0.3 °C—parameters compatible with active inflammatory processes and perfusion heterogeneity.[16] The thermographic pattern characterized by alternating areas of hyperperfusion and hypoperfusion suggests endothelial dysfunction and microvascular remodeling, findings that align with the work of



ROI	Máx °C	Min °C	Méd °C	Ampl °C	d.p. °C	s²	T1	T2
r1	33.25	30.50	32.10	2.75	0.50	0.25	6.10	4.10
r2	33.20	31.74	32.48	1.46	0.26	0.07	6.48	4.48

Delta	Máx °C	Min °C	Méd °C	Ampl °C	d.p. °C	s²	T1	T2
r1-r2	0.05	-1.24	-0.38	1.29	0.24	0.19	-0.38	-0.38

ROI	Máx °C	Min °C	Méd °C	Ampl °C	d.p. °C	s²	T1	T2
r1	33.21	29.72	31.57	3.49	0.64	0.41	5.57	3.57
r2	32.18	29.87	30.97	2.31	0.60	0.36	4.97	2.97

Delta	Máx °C	Min °C	Méd °C	Ampl °C	d.p. °C	s²	T1	T2
r1-r2	1.03	-0.15	0.60	1.18	0.04	0.05	0.60	0.60

Fig 2. Thermographic findings in patients with lipedema. **(A)** Anterior view demonstrating increased surface temperature in the infragluteal and lateral thigh regions, consistent with inflammatory activity. **(B)** Lateral view highlighting focal areas of increased heat emission corresponding to regions of enhanced vascularization. Quantitative thermographic parameters (ROI 1 and ROI 2) demonstrate measurable temperature asymmetry and increased thermal amplitude, supporting a hypermetabolic inflammatory pattern. *ROI*, region of interest.

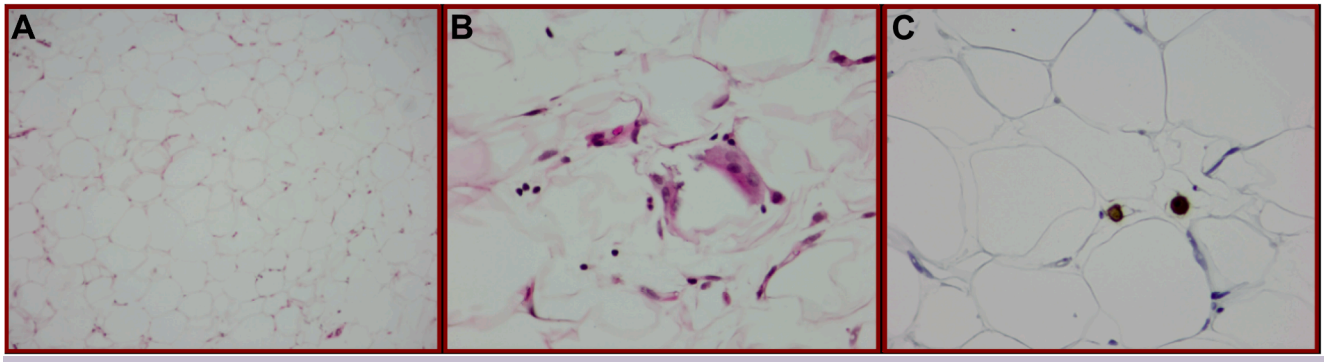


Fig 3. Histological findings in lipedema tissue. **(A)** Adipocyte hyperplasia observed in all patients, with enlargement and an increased number of adipocytes in subcutaneous tissue hematoxylin and eosin (H&E). **(B)** Cytosteatonecrosis identified in 30% of patients, characterized by adipocyte membrane disruption, lipid vacuole collapse, and inflammatory infiltrate H&E. **(C)** Increased number of mast cells (≈60%) evidenced by metachromatic staining (Giemsa), indicating chronic inflammatory activity.

Michelini et al,[8] who documented capillary wall thickening, endothelial and pericytic hyperplasia, and degenerative changes in adipose tissue affected by lipedema.

Functional findings from thermography also correlate with studies of cutaneous physiology, demonstrating that sustained thermal variations reflect alterations in capillary flow regulated by nitric oxide and autonomic mechanisms.[17] Thus, the thermal heterogeneity observed in this study likely represents regions of compensatory vasodilation interspersed with areas of microvascular stasis.

The low-grade inflammatory profile identified histologically—characterized by increased mast cell counts and mild fibrosis—is consistent with the microenvironment described by Felmerer et al,[10] who reported elevated vascular endothelial growth factor C levels and macrophage infiltration without major lymphatic structural changes, and with Grewal et al,[6] who identified M2-polarized macrophages as regulators of adipose expansion and angiogenesis in lipedema.

From an anatomical perspective, the findings of Cestari[18] demonstrating thickening of the superficial fascia, hypertrophy of interlobular septa, and subfascial fluid accumulation correspond to the hypoperfused, cooler areas detected by thermography and the regions of slow microvascular flow identified by MFI. Together, these observations reinforce the concept of lipedema as a vasculofascial disease rather than a purely adipose disorder.

Furthermore, the increase in interstitial fluid and early angiogenesis described by Allen et al[11] and Duhon et al[1] support the "fluid-fat-fibrosis" model, in which protein-rich interstitial congestion activates fibroblasts and promotes neovascularization. The detection of elevated platelet factor 4 levels in patients with lipedema, as reported by Ma et al,[12] further consolidates the lymphovascular component of this pathophysiology.

Finally, imaging studies in inflammatory skin conditions such as psoriasis have demonstrated that changes in RI and blood flow patterns reflect microvascular endothelial dysfunction, reinforcing the applicability of hemodynamic analysis for detecting inflammatory activity in lipedema as well.[19,20]

Taken together, these findings indicate that lipedema presents distinct microvascular characteristics detectable by functional imaging techniques, in which MFI and infrared thermography act in a complementary manner: MFI captures microvascular morphology and flow dynamics, while thermography reflects the thermal consequences of abnormal tissue perfusion.

These findings suggest that MFI and thermography may serve as noninvasive biomarkers of disease activity rather than screening tools. Such parameters may assist in differentiating lipedema from overlapping conditions and may be useful for monitoring disease progression in future longitudinal studies.

Limitations. The main limitations of this study include the small number of participants and the absence of a control group, restricting the generalizability of the findings and preventing inferential statistical analysis. Because the study was designed to evaluate intrasubject correlation between imaging and histology rather than diagnostic discrimination, comparisons with BMI-matched individuals were not performed. However, the consistent qualitative correlation observed between imaging findings and histological alterations can provide a rationale for future prospective, controlled, multicenter studies with stratification by clinical stage and the combined use of MFI, infrared thermography, and automated histomorphometric analysis.

CONCLUSIONS

Lipedema is associated with microvascular and thermal alterations that can be identified using noninvasive

imaging techniques and that correlate with histological findings of angiogenesis, increased capillary density, and chronic inflammation.

The combination of ultrasound with MFI and infrared thermography allows integrated characterization of microvascular activity and may represent a promising tool for differential diagnosis and for monitoring clinical progression in patients with lipedema.

AUTHOR CONTRIBUTIONS

Conception and design: FB, NO, PL, LM, RJ
Analysis and interpretation: FB, NO, LM, RJ
Data collection: FB, PL, LM, RJ
Writing the article: FB, NO
Critical revision of the article: FB, NO, PL, LM, RJ
Final approval of the article: FB, NO, PL, LM, RJ
Statistical analysis: FB
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Overall responsibility: FB

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with solely to assist with language translation and to improve fluency and readability of the manuscript text. After using this tool, the authors carefully reviewed and edited the content as needed and take full responsibility for the accuracy, integrity, and content of the publication.

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DISCLOSURES

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